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On January 20, 2000

By: Andrea Gill

PATENT
Atty. Docket No.(TTC): 19904-002-1US
Client Reference (Stanford) No. 97-104
Attorney Docket No.(BFF)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: William Jarvis
SCHATZBERG & BELANOFF	Art Unit: 1614
Application No.: 09/244,457	
Filed: February 4, 1999	DECLARATION OF DR. JOSEPH BELANOFF UNDER 37 C.F.R. §1.132
For: METHODS FOR TREATING PSYCHOSIS ASSOCIATED WITH GLUCOCORTICOID RELATED DYSFUNCTION	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Joseph Belanoff, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. Exhibit 1, attached hereto, is incorporated herein by reference.

2. I received an M.D. in 1992 from Columbia University, College of Physicians and Surgeons.

3. I am presently employed at Stanford School of Medicine where I am conducting research to improve medical treatment for people suffering from psychosis. I am also the CEO of Corcept, Inc., whose primary mission is to provide improved medicine for psychiatric illnesses.

4. I have read and am familiar with the contents of the application. I understand that the Examiner has a rejection under §103 based upon his belief that one of skill reading the prior art of Ravaris, van der Lely, Piazza *et al.*, and Behl *et al.*, would have a reasonable expectation that patients with psychotic major depression [PMD] would be treatable with a glucocorticoid type II receptor antagonist.

5. We have conducted clinical trials which demonstrate that the invention was unpredictable. This unpredictability is demonstrated in two clinical trials that we conducted and that were reported to the Food and Drug Administration by way of an Annual Progress Report filed pursuant to an Investigational New Drug Application. A copy of that report is attached as **Exhibit 1.** In this report, the glucocorticoid receptor antagonist, mifepristone, is cited as being effective for treating psychosis in patients suffering from psychotic major depression and as having no clinical benefit for psychotic patients suffering from schizoaffective disease. The clinical studies were conducted by myself or at my direction.

6. Mifepristone for treating Psychotic Major Depression [PMD].

This study established that mifepristone was effective in treating psychosis in 4 out of 5 patients with the least psychotic patient being the least amenable to treatment. While all patients had improvement in the HAM-D depression test, the patients remained depressed and the improvement was attributed to the reduction in the level of psychosis.

The subjects were five newly admitted patients with an admitting diagnosis of major depression with psychotic features (DSM-IV criteria). The diagnosis at admission was confirmed independently by two psychiatrists. The subjects served as their own controls in a cross-over design. They were given either 600mg of mifepristone for four days, followed by four days of placebo; *or,* four days of placebo, followed by 600mg of mifepristone. Both the patients and the investigators were blind to which compound the patient was receiving. Routine biological and hematological studies were conducted daily in order to watch for evidence of relative adrenal insufficiency, such as hypoglycemia and eosinophilia.

The subjects had to be between the ages of eighteen and seventy-five, and without major medical problems. Patients were excluded if they had any signs of the Cushing Syndrome. Furthermore, because mifepristone in the dose range we used is reported to cause an abortion rate approaching eighty-five percent, women of childbearing potential were excluded from the study. All patients who admitted to having used illicit drugs within the month prior to admission, or who consumed in excess of two ounces of alcohol daily were also excluded.

Patients did not take anti-psychotic medication within three days of entering the study. No patients were taking antidepressant medication at the time they entered the mifepristone trial. No patient was *started* on an antidepressant medication while participating in the study. Benzodiazepines were permitted for insomnia and acetaminophen for headaches. If a patient's condition was such that they could not tolerate the drug-free period (for example, if they were intensely suicidal), they were

not studied. Finally, all patients were required to give written consent to a protocol approved by the Institutional Review Board at Stanford University Medical Center.

Formal psychiatric assessments (including the Hamilton Rating Scale for Depression[1] (HAM-D), Brief Psychiatric Rating Scale (BPRS) which measures psychosis, and Clinical Global Impression (CGI)), were carried out on days one, three, five, seven, and nine at 1000. On days one, five, and nine, paragraph recall was tested at 1130. Cortisol levels were measured serially every half-hour from 1300 to 1600, and plasma ACTH and plasma HVA were measured serially every hour from 1300 to 1600. Blood samples were spun down and plasma were frozen at -80°F in the General Clinical Research Center Laboratory. Plasma cortisol determinations were made by radioimmunoassay (RIA) in the Endocrinology Laboratory at Brigham and Women's Hospital (Harvard University). Plasma ACTH was assayed by immunoradiometric assay (IRMA) in the same laboratory.

FIGURE 1: EXAMPLE TIMELINE FOR A PATIENT WHO RECEIVED MIFEPRISTONE FIRST (DOUBLE BLIND STUDY).

DAY 1	
10:00	Psychiatric Assessments (HAM-D, BPRS, CGI)
11:30	Paragraph Recall
13:00-16:00	Afternoon Cortisol Test
13:00-16:00	Plasma ACTH & HVA

[1] Hamilton M: A Rating Scale for Depression. *J Neurol Neurosurg Psychiat* 1960; 23:56-62.

Day 2	Subject started on 600mg mifepristone
Day 3 10:00	600mg mifepristone Psychiatric Assessments (HAM-D, BPRS, CGI)
Day 4	600mg mifepristone
Day 5 10:00 11:30 13:00-16:00 13:00-16:00	600mg mifepristone Psychiatric Assessments (HAM-D, BPRS, CGI) Paragraph Recall Afternoon Cortisol Test Plasma ACTH & HVA
Day 6	600mg Placebo
Day 7 10:00	600mg Placebo Psychiatric Assessments (HAM-D, BPRS, CGI)
Day 8	600mg Placebo
Day 9 10:00 11:30 13:00-16:00 13:00-16:00	600mg Placebo Psychiatric Assessments (HAM-D, BPRS, CGI) Paragraph Recall Afternoon Cortisol Test Plasma ACTH & HVA

BRIEF PATIENT HISTORIES

PATIENT 1

This 50-year-old man had no prior psychiatric history, and had received no mental health treatment except for "career counseling" in graduate school. He was employed as an executive in the high-tech industry, was in excellent physical health, and was married with no children. He took no medications other than daily vitamins. Three months prior to his entry into the study he noted increasing feelings of depression with anhedonia, insomnia, decreased appetite, and decreased concentration. A stressor at that time was his mother's entry into a skilled nursing facility because of advanced

Alzheimer's Disease. One month prior to entry into the study, he began to grow increasingly suspicious that co-workers were talking about him and "planning to get him fired." At entry into the study, he was extremely guarded with mood-congruent delusions that the hospital might be a prison where he would be executed. He had received no psychiatric care to that point.

At admission, the subject's mean afternoon cortisol level was 12.0μg/dL, and did not decline throughout the afternoon collection period. He received mifepristone first, and by day 5 his mean afternoon cortisol level was 37.7μg/dL; and, in a striking example, the normal rhythm of a steady decline of cortisol levels throughout the afternoon had resumed (see Table 1). His HAM-D declined from 29 to 21, and his BPRS declined from 47 to 40. Moreover, from day 5 to day 9, while on placebo, his HAM-D continued to drop (21 to 10), as did his BPRS (40 to 25), suggesting that mifepristone continued to be active in his system, as indicated by the continued elevation of his afternoon cortisol values. At this time, his normal cortisol rhythm continued. The patient experienced no adverse effects and no lab values other than cortisol, and ACTH changed significantly. The patient was started on the antidepressant, paroxetine, at discharge and returned to work two weeks later. His depressed mood resolved over the next several weeks and his paroxetine was discontinued nine months after conclusion of the study. He remains asymptomatic two years later.

Table 1: Results of the Afternoon Cortisol Test (Patient 1)

Time	Day 1 Cortisol Levels (μg/dL)	Day 5 Cortisol Levels (μg/dL)	Day 9 Cortisol Levels (μg/dL)
1300	11.8	56.0	22.1
1330	14.4	40.9	22.7
1400	11.6	34.4	16.9
1430	10.4	34.2	14.1
1500	11.6	34.6	13.4
1530	12.7	35.7	12.6
1600	11.8	28.4	18.7
Mean	12.0μg/dL	37.7μg/dL	17.2μg/dL

PATIENT 2

This subject was a 44 year-old European-American woman with a history of one prior episode of PMD; three years prior to study admission, she had been hospitalized for one week with florid symptoms of depression and psychosis. During her initial episode of PMD she acknowledged being very depressed and felt that the devil was controlling her. She knew this to be true because her bed was very cold and there "might have been a machine under [her] bed." Against medical advice, she left the hospital because she came to believe that one of her physicians was also being controlled by the devil. After leaving the hospital, she continued to be severely depressed with both auditory hallucinations as well as somatic delusions. She tried paroxetine for several weeks but there was no change in her condition. The paroxetine was decreased and nortriptyline was started. Eventually, lithium was added to her treatment regimen, and her depression improved, although her somatic delusions remained.

One year prior to study admission she found that all of her symptoms had resolved. Two months later, against medical advice, she decided to discontinue taking medications. For nine months she remained asymptomatic, but then became depressed again. She could not identify any particular precipitating event. She reported increasingly depressed mood, weight loss, decreased concentration, memory, and energy, anhedonia, and insomnia.

One month after the onset of this depressive episode she attempted suicide by hanging. The attempt failed because her feet reached the floor. She then made a second suicide attempt by taking an overdose of the previously prescribed nortriptyline. At this point, she was brought to the Emergency Department and stabilized. During her exam, she revealed that she had recently been hearing strange noises in her house and "seeing shadows." She also stated that "the devil [was] manipulating her body" and that she had been unwilling to drive because "the devil [had] the power to destroy her." Her exam in the Emergency Department was also notable for significant psychomotor retardation.

Prior to her first hospitalization, the subject had no psychotic history. She immigrated to the U.S. in 1992, has been married for 21 years, has two children, and works as a domestic. Her only long-standing medical problems are irritable bowel syndrome and back pain. Her family history includes one sister who suffers from "mood swings," and her father who suffers from alcoholism. At the time of study entry, the subject's physical exam was within normal limits, and she was on estradiol and medroxyprogesterone for perimenopausal symptoms.

The subject received placebo first, and then mifepristone. While on placebo, her HAM-D increased from 33 to 35 and her BPRS from 51 to 57. While on mifepristone, her HAM-D declined from 35 to 21 and her BPRS from 57 to 44. At the end of the nine-day study, the subject was no longer delusional and felt well enough to go home. She declined follow-up antidepressant medication. Six weeks after leaving the study, she was reported to be suffering from symptoms of PMD and did not return for follow-up.

PATIENT 3

The subject, a 67 year-old woman with a history of recurrent PMD, was admitted after taking 15 fluoxetine capsules in a suicide attempt. Her first episode of PMD was in 1980 during which she suffered from delusions of persecution and reference, and was hospitalized following a suicide attempt. One year prior to study entry she suffered from an episode of PMD and was prescribed a low dose of haloperidol and fluoxetine. Her condition improved to the point where she felt "back to normal," and after 2 to 3 months of combination therapy she decided to stop taking her prescribed haloperidol and fluoxetine. Two months prior to study admission, her condition began to deteriorate. She complained of very low energy, poor appetite, spontaneous crying, poor self-care, and increased guilt about being a burden to her family. She also expressed increasingly delusional thoughts including that her phones were tapped, her family was trying to poison her, her neighbors were observing her through her windows; and, most recently, that white automobiles were following her. There was a question of whether she suffered from auditory hallucinations because she

complained of hearing "sirens" and "phones ringing," but this observation was complicated by her partial hearing loss.

The subject's psychiatric history has been marked by long periods when she is fully functional (working as a nursing aide) with intermittent episodes of severe depression and paranoid ideation. At admission, the subject was taking no medications of any kind on a regular basis. Other than a 65% hearing loss in one ear, and a 35% loss in the other ear, she had no ongoing medical problems.

This subject received placebo first and then mifepristone. While on placebo her HAM-D declined from 23 to 19 and her BPRS increased from 32 to 35. While on mifepristone, her HAM-D declined from 19 to 17 and her BPRS increased from 35 to 36. She was discharged on olanzapine and her condition continued to improve. Her mean afternoon cortisol was 9.4μL/dL at entry into the study, 9.4μL/dL after four days of placebo, greater than 60μL/dL after four days of mifepristone, but only 3.1μL/dL when she returned for a follow-up eight weeks later and was feeling well.

PATIENT 4

This subject was a 57 year-old male physician with an 18-month history of severe depression characterized by extreme insomnia, low energy, poor concentration, and somatic concerns that had resulted in an extensive medical work-up. Despite an extraordinary physical workup, he could not be convinced that he was physically sound and planned even more extensive physical testing. He tried virtually all of the antidepressants currently available, often in combination with antipsychotic

medication. He also had a round of ECT therapy, with 8 treatments that led to a mild diminution of symptoms that quickly faded. He had not been able to work for the past 15 months, which was in sharp contrast to a very productive career prior to the onset of his depression. He linked the onset of his depression to treatment with prednisone for an allergic reaction. He had no prior history of depression and no medical problems, but his family history was significant for his mother having severe late-life depression. He had weaned himself of all medications (with the exception of clonazepam for sleep) prior to study entry.

The subject received placebo first. While on placebo his HAM-D declined from 31 to 28 and his BPRS declined from 53 to 45. While on mifepristone his HAM-D declined from 28 to 21 and his BPRS from 45 to 28. He left the hospital at the end of the study and was started on venlafaxine, a treatment to which his depression had not previously responded. Although his course of recovery was not a straight line, his improvement continued over time and he required neither further hospitalization nor ECT to eventually gain full recovery.

PATIENT 5

This subject was a 45 year-old man with a history of obsessive-compulsive disorder. In the 8 months prior to study entry, he became increasingly depressed, suffering from poor sleep, anhedonia, poor concentration, low energy, and feelings of guilt, and had developed a fixed belief that his hearing had been irreparably harmed by various noises in his environment. These noises included a phone ringing, a child's bell, and a car horn. He became convinced that he had lost "almost all" of his

hearing and was not dissuaded by the many trips to the audiologist, which indicated normal hearing, nor by the fact that he could converse in normal tones with those around him. Several weeks before study admission, he contemplated suicide and was briefly involuntarily hospitalized because he was a danger to himself. After trying a first dose of several medications, he refused to take any medication because he believed that each previous one or two pill trials had added to his hearing loss. Shortly before study admission, he began to "sense" that the police were "trailing him" ever since his involuntary admission. This subject worked as a college professor, and was married with three children. He used no illicit substances or alcohol, but did have a family history of several siblings with major depression, his mother suffered from both depression and dementia prior to her death.

This subject received mifepristone first and then placebo. While on mifepristone, his HAM-D declined from 46 to 37 and his BPRS from 54 to 41. Of note is that item 11 (suspiciousness) declined from a "6", severe, to a "1", absent, and item 15 (unusual thought content) declined from a "6" to a "3", mild. He no longer believed that the "police [were] trailing him" nor that his phone was tapped. However, he still obsessively believed that he had a hearing loss, and his desire to have his hearing re-tested was even stronger than before. While on placebo his HAM-D declined from 37 to 35, but his BPRS increased again from 41 to 54, with particularly high scores on "somatic concern" and anxiety. At discharge he refused all medications, and he has remained quite debilitated with high levels of somatic anxiety.

Results

Table 2: Individual HAM-D Scores

Subject #	Day 1	Day 5	Day 9
1 (mifepristone first)	29	21	10
2 (placebo first)	33	35	21
3 (placebo first)	23	19	17
4 (placebo first)	31	28	21
5 (mifepristone first)	46	37	35

In all cases, HAM-D scores declined during mifepristone treatment. In both cases, where the subject received mifepristone first, their HAM-D declined farther during the placebo treatment than if placebo received first (case one significantly, case five marginally). In the three cases where placebo was given first, HAM-D scores changed very little (rising slightly in case two and falling slightly in cases three and four.) Ignoring the carryover effect leaves five active treatment cells and three placebo cells. The mean decline in HAM-D while on mifepristone was 8.4 (31%) while on placebo it was 1.2 (7%). The difference approaches statistical significance ($F = 5.01$, $p<.07$).

Table 3: Individual BPRS Scores

Subject #	Day 1	Day 5	Day 9
1 (mifepristone first)	49	40	25
2 (placebo first)	51	57	44
3 (placebo first)	32	35	36
4 (placebo first)	53	45	28
5 (mifepristone first)	54	41	54

In all cases but one, BPRS scores declined during mifepristone treatment. (The exception was case three, the patient with the lowest BPRS at study

entry. Her BPRS score increased by one point.) In one case where the subject received mifepristone first (case one) their BPRS continued a distinct decline during the placebo period. In the other subject who received mifepristone first (case 5), the subject's BPRS reversed to the pretreatment level during placebo treatment. The mean decline in BPRS score was 10.6 points (32.5%) while on mifepristone, while BPRS increased .3 points (.5%) while the subjects were on placebo. The difference again approaches statistical significance ($F = 4.31$, $p<.08$).

Conclusion: All the patients were discharged from the hospital at the end of the nine-day study period. All of the five subjects showed significant improvement in their HAM-D scores while on mifepristone and four of the five subjects share improvement in their BPRS scores. Moreover, the subject who did not was the least symptomatic to start. The 32.5% overall decline in BPRS approaches the 40% value frequently seen in six to eight week trails of effective antipsychotic medication. None of the subjects reported side effects of any kind, and both basic lab measures and measures of vital signs were unaffected by treatment.

While HAM-D [psychosis] scores diminished during treatment, all the patients still had significant residual signs and symptoms of major depression. We recommend that all patients begin antidepressant treatment at the end of the study. We observed that the more significant clinical change was that 4 of the 5 patients were no longer psychotic at the end of the study and all were more cognitively organized. The reason that the patients' HAM-D scores declined was apparently due to their being more cognitively intact and because they felt in better control of their thinking.

7. Schizoaffective disorder tests did not work.

As reported in the attached letter (Exhibit 1) to the FDA, we did a double-blind, placebo controlled clinical trial for patients having been diagnosed with schizoaffective disorder. This disease describes a patient who is suffering from both schizophrenia and mood disorders, most typically depression. In this study, both psychotic patients suffered from depression. The results of the study are provided below in Table 4. All scoring was done by blinded raters who were not staff members.

In the first round of the trial, both patients were given placebo and no effect on their BPRS scores were noted. After completion of the study, the patients were given the option and elected to try mifepristone in an open-label study. Despite the increased likelihood that the patients would respond because they and the staff knew that they were receiving mifepristone, neither patient demonstrated any improvement in BPRS.

Table 4
TREATMENT OF SCHIZOAFFECTIVE DISORDER USING MIFEPRISTONE

Subject No.	Scale	Day 1 (raw score)	Day 9 (raw score)	Δ
1 (placebo)	HAM-D	24	17	-7
	BPRS	47	53	+6
	CGI	4 (moderately depressed)	5 (markedly depressed)	+1
2 (placebo)	HAM-D	33	30	-3
	BPRS	51	46	-5
	CGI	4 (moderately depressed)	4	0

OPEN-LABEL STUDY OF THE TREATMENT OF SCHIZOAFFECTIVE DISORDER USING MIFEPRISTONE

Subject No.	Scale	Day 1 (raw score)	Day 9 (raw score)	Δ
1	HAM-D	15	15	0
	BPRS	40	39	-1
	CGI	3 (mildly depressed)	4 (moderately depressed)	+1
2	HAM-D	28	21	-7
	BPRS	50	49	-1
	CGI	4 (moderately depressed)	4	0

This Declarant has nothing further to say.

Dated: January 11, 2000

Joseph Belanoff, M.D.

Attachment: Exhibit 1

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